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INTRA-ABDOMINAL INFECTIONS, HEPATITIS, AND GASTROENTERITIS (T STEINER, SECTION EDITOR)

HBV Reactivation in Patients Receiving Bruton Tyrosine Kinase Inhibitors (BTKIs): a Systematic Review and Meta-Analysis

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Abstract

Purpose of Review Bruton tyrosine kinase inhibitors (BTKIs) are immunosuppressive cancer therapies approved for the treatment of various mature B-cell malignancies. Hepatitis B virus reactivation (HBVr) is a known complication in patients with chronic or past HBV infection undergoing immunosuppressive chemotherapy. The present work aims to establish the correlation between HBVr and patients receiving BTKIs.

Recent Findings This review included 18 studies. The overall incidence of HBVr was found to be 6.6% in patients with past HBV infections who received ibrutinib. Fourteen cases of HBVr were associated with ibrutinib (two occult hepatitis B infections and twelve past HBV infections). One case of HBV past infection was associated with zanubrutinib, and three cases were recorded for acalabrutinib (one chronic HBV and two past HBV). Most incidents occurred in males older than 60 years within the first year after initiating BTKIs. Three reported cases documented HBVr after discontinuing ibrutinib and zanubrutinib. Two deaths caused by HBVr in patients with past HBV infections were recorded (one for each of acalabrutinib and ibrutinib). Remarkably, HBV antiviral treatment normalized liver functions and eliminated serum HBV in most cases. It was reported that false negativity of HBsAg following reactivation occurred in two cases: one case was attributed to HBsAg escape mutations, and the other to the hook effect.

Summary Our findings show that HBVr risk is intermediate in patients with past HBV infections who receive ibrutinib. Universal anti-HBV prophylaxis before initiating ibrutinib may be an option.

Keywords Bruton tyrosine kinase inhibitors · BTKIs · Ibrutinib · Zanubrutinib · Acalabrutinib · Hepatitis B virus reactivation · HBVr · Systematic review · Meta-analysis

Abbreviations

BTKIs	Bruton tyrosine kinase inhibitors
HBVr	Hepatitis B Virus reactivation
HBV	Hepatitis B Virus
AGA	The American Gastroenterology Association
APASL	The Asian Pacific Association for the Study of the Liver
ECIL-5	The European Conference on Infection in Leukemia
ASCO	The American Society of Clinical Oncology

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R/R MCL	Relapsed/Refractory Mantle Cell Lymphoma
HBsAg	Hepatitis B surface antigen
HbcAb	Hepatitis B core antibody
AASLD	American Association for the Study of Liver Diseases
CLL	Chronic lymphocytic leukemia
MCL	Mantle cell lymphoma
MZL	Marginal zone lymphoma
WM	Waldenström macroglobulinemia

Introduction

The progression of hepatitis B virus (HBV) infection is influenced by the dynamic interaction between viral replication and the immunological response of the host [1]. Even in patients showing serological recovery, HBV can be detected in the hepatocytes and peripheral blood mononuclear cells. As a result, the reactivation of HBV has been reported in individuals undergoing immunosuppressive therapy, leading to significant clinical outcomes such as hepatitis flare, decompensation, and hepatic failure [2•, 3].

The occurrence of HBV reactivation (HBVr) is influenced by the disruption of the interplay between the host immune system and HBV replication [2•]. Any form of immunosuppression impairs host immune-mediated control of viral replication, potentially leading to HBVr. Immunosuppressive therapies, such as medications depleting B or T cells, chemotherapeutic agents, corticosteroids, and other biologics, can potentially induce host immunological dysfunctions, inhibiting the immune response to HBV [2•].

The American Gastroenterology Association (AGA) and The Asian Pacific Association for the Study of the Liver (APASL) have implemented a risk stratification strategy for HBVr based on the type of therapy administered [4•, 5]. According to this classification, patients undergoing immunosuppressive therapy are categorized as follows: high risk if the reactivation rate is 10%, moderate risk if the rate falls between 1 and 10%, and low risk if the reactivation rate is less than 1% [4•, 5].

APASL, AGA, the European Conference on Infection in Leukemia (ECIL-5), and the American Society of Clinical Oncology (ASCO) provide valuable guidelines on HBV screening, management, and recommendations for HBV prophylaxis for patients preparing to undergo systemic anticancer therapy [4•, 5, 6, 7••]. However, currently, there is no recommendation for novel targeted cancer therapies referred to as Bruton Tyrosine Kinase Inhibitors (BTKIs), as the degree of risk of HBVr has not yet been established.

Ibrutinib, the first effective and selective BTKI, received FDA approval as a breakthrough therapy for relapsed/refractory mantle cell lymphoma (R/R MCL). Thereafter, the FDA approved ibrutinib for relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (R/R CLL/SLL), naïve CLL/SLL, relapsed/refractory marginal zone lymphoma (R/R MZL), Waldenström macroglobulinemia (WM), and relapsed/refractory chronic graft-versus-host disease (R/R cGVHD). In 2017 and 2019, the second-generation BTKIs, acalabrutinib and zanubrutinib, were respectively approved for R/R MCL to reduce off-target effects. The mechanism of BTKIs involves blocking the activity of the BTK enzyme, disrupting BCR signaling, and inhibiting B cell activation and antibody production [8].

In clinical practice, physicians exhibit a heterogeneous attitude regarding antiviral prophylaxis for HBV DNA-negative, HbsAg-negative, and negative/anti-positive patients receiving BTKIs. There is a need to consolidate our knowledge from individual research regarding the degree of risk of HBV reactivation in patients receiving BTKIs. Thus, we conducted this systematic review with a meta-analysis to address the limitations of individual research and resolve the discrepancies in its conclusions. The objective of our study is to synthesize the risk of HBVr in patients receiving BTKIs, assess the time interval of reactivation, identify the characteristics of patients who experience HBVr, and elucidate the resulting clinical consequences of such reactivation events. Lastly, we highlight the knowledge gaps that need further research to address.

Methods

Definitions

We adopted the ASCO definitions for chronic HBV infection, past HBV infection, and the clinical outcomes of HBVr, including HBV-associated hepatitis flare, HBV-associated liver failure, and death attributed to HBVr [7••]. According to ASCO, HBVr in patients with past HBV infection is defined as one of the following: (1) HBV DNA becoming detectable or (2) reverse HBsAg seroconversion (reappearance of HBsAg). For patients with chronic HBV infection, HBV reactivation is defined as one of the following: (1) an increase of ≥ 2 log (100-fold) in HBV DNA compared to the baseline level; (2) HBV DNA ≥ 3 log (1000) IU/mL in a patient with previously undetectable HBV DNA, or (iii) HBV DNA ≥ 4 log (10,000) IU/mL if the baseline level was not available [7••]. Occult hepatitis B infection is defined as the presence of hepatitis B virus (HBV) DNA in the liver, even though individuals test negative for HBsAg (hepatitis B surface antigen) using currently available assays [9]. In cases of occult infection, the presence of HBV DNA in the serum may be detectable or undetectable. When detectable, the level of HBV DNA in the serum is typically very low, often measuring less than 200 IU/mL [9].

Search Strategy

A comprehensive literature search was conducted from inception up to August 2023 across the following databases: MEDLINE [PubMed], Scopus, Google Scholar, and Web of Science. The search utilized the following keywords: ("HBV reactivation" OR "hepatitis B reactivation" OR "viral hepatitis reactivation" OR "reactivation of HBV") AND ("BTKIs" OR "Bruton kinase inhibitors" OR "ibrutinib" OR "acalabrutinib" OR "zanubrutinib"). Additionally, the reference lists of the included studies were scanned to ensure a comprehensive representation of the existing literature. The checklist of items to include when reporting a systematic review or meta-analysis is presented in Table S1.

Eligibility Criteria

Studies were included if they met all the following criteria:

1. Reported the occurrence of HBV reactivation or case reports characterizing HBVr in patients receiving BTKIs.
2. Presented baseline HBV marker data before the initiation of BTKIs.

Studies were excluded if they lacked baseline data on HBV markers or described HBVr in patients who received immunosuppressive chemotherapy other than BTKIs.

Patients on anti-HBV medication, studies in which the clinical definition of HBV reactivation was not mentioned, and patients who had BTKIs added to anti-CD-20 were omitted from the data synthesis due to the potential risk of bias in estimation. However, they were included in the systematic review.

Two independent reviewers screened eligible articles from the electronic search outputs based on the aforementioned inclusion and exclusion criteria. Disagreements were solved by discussion and consensus between the two reviewers.

Data Extraction

The data extraction process involved the collaboration of two independent reviewers who gathered the necessary information. To ensure accuracy and reliability, the extracted data was subsequently cross-checked by another reviewer. From each study included in the analysis, the following key details were carefully documented: the author's name and publication date, the definition of reactivation, the number of recruited patients, the types of hematologic malignancies examined, the specific BTKIs used, baseline HBV markers, follow-up duration, and the count of reactivation events.

From each case of HBVr, the following pertinent information was extracted: the author's name, publication date, age of the patient, sex, the specific BTKIs administered, the timing of reactivation in relation to the initiation of BTKIs, the baseline status of hepatic markers, the type of HBV infection, details regarding HBVr, HBV antiviral treatment received, the clinical outcome of the patient, and the ultimate outcome of the treatment provided. These essential data points were systematically collected to enable a comprehensive analysis and interpretation of the HBVr cases and their associated factors.

Bias Assessment

The bias of the included studies was evaluated by two independent reviewers using a checklist comprising several key items (Table S2). Firstly, the adequacy of the sample size was assessed to ensure that it was sufficient for drawing meaningful conclusions. Secondly, the presence of a clear definition for HBVr was required. Thirdly, the reviewers assessed the adequacy of the follow-up period. Fourthly, the baseline data on HBV markers (HBsAg, HBcAb, and HBV DNA level) were clearly stated. Lastly, the reviewers considered whether there had been any prior use of anti-CD20 therapy within the last year, as this information could potentially influence the occurrence of HBVr. Through this comprehensive checklist, we aimed to identify and address any potential biases in the included studies. Disagreements between the two reviewers were fixed through discussion and shared agreement, and when necessary, any disagreement between reviewers was fixed through discussion with a third reviewer.

Data Synthesis

The results were presented as proportions with a 95% confidence interval (CI), calculated using the random effects model. Heterogeneity between the studies was assessed using I-squared and Cochran's Q statistics. Sensitivity analysis was conducted using the leave-one-out approach to assess results robustness. All statistical analyses were performed using Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA).

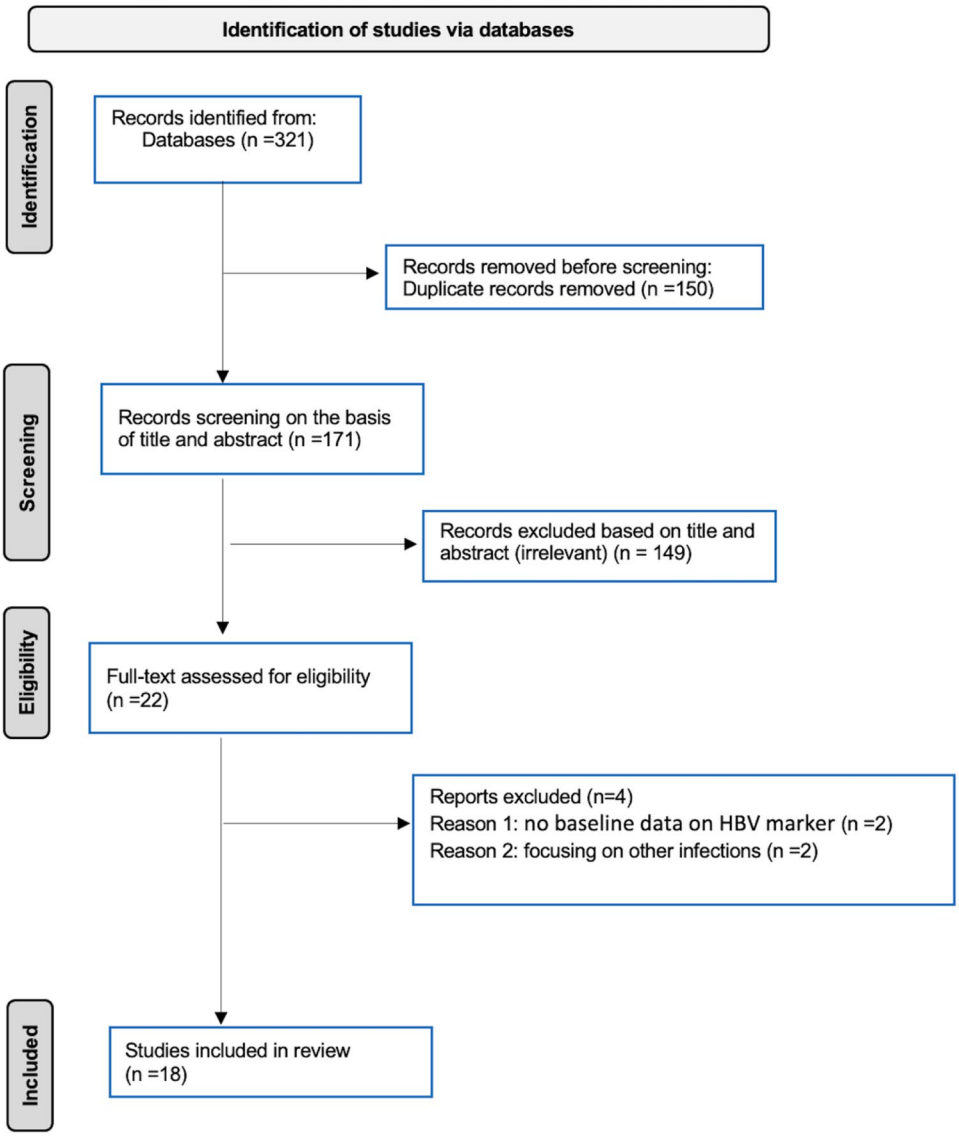

Fig. 1 Flow chart depicting the selection of publications

Results

Study Selection and Characteristics of Included Studies

A total of 321 titles were identified through database searches, of which 18 were included in this review (Fig. 1) [10–16, 17•, 18, 19••, 20–27]. The current systematic review thus comprises 18 studies, including 10 case reports and 8 observational studies.

The Pooled HBVr in Patients with HBV Past Infections Receiving Ibrutinib

Among the eight observational studies [12–16, 17•, 18, 19••], five with a low risk of bias were included in the meta-analysis. The other three studies had a relatively high risk of bias, as presented in Table S2 [13–15]. The pooled prevalence of HBVr in patients with HBV past infection from the remaining five studies is 6.6% (95% CI, 2.9–14.6) (Fig. 2A). The duration of reactivation spanned from 2 [19••] to 42 months [18]. Table 1 represents the characteristics of the eight studies. The sensitivity analysis demonstrated the robustness of the overall prevalence (Fig. 2B), indicating that it is not influenced by any individual study.

The HBVr in Patients with HBV Past Infections Receiving Acalabrutinib and Zanubrutinib

There was a single report that characterized HBVr in patients with a history of HBV infection who were treated with zanubrutinib and acalabrutinib. This report, authored by Chiu et al. [19••], described one case of reactivation among 14 patients (7.1%) with past HBV infection who received

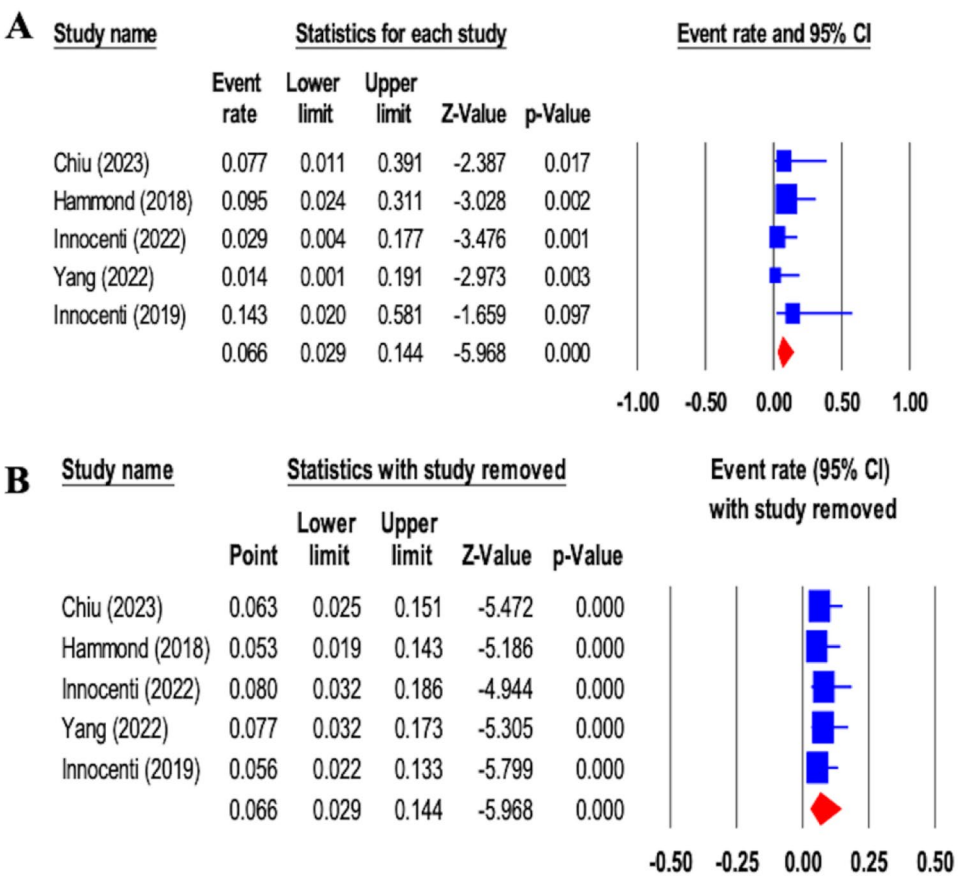

Fig. 2 The pooled HBV reactivation in patients with HBV past infections receiving ibrutinib. **A** Forest plot, **B** sensitivity analysis using leave-one-out approaches

acalabrutinib. Interestingly, no cases of reactivation were observed in the one patient who received zanubrutinib.

HBVr in Patients with HBsAg-Positive Infection

Two reports described HBVr in patients with chronic HBV infection. Chiu et al. [19••] reported that among patients who received acalabrutinib without HBV prophylaxis, one out of one (1/1) with chronic HBV infection experienced HBVr. In contrast, Ni et al. [13] observed no reactivation in four patients with chronic HBV infection (0/4) who received entecavir as a preventive measure before receiving BTKIs.

HBVr in Patients with HBV Past Infection on Prophylaxis Therapy Compared with Those Without HBV Prophylaxis

Two studies addressed HBVr among patients who received prophylaxis with lamivudine before ibrutinib administration and continued during the study follow-up period [12, 17•].

In one study, HBVr in the prophylaxis group was occurred in 1/73 patients (1.4%) compared to 1/35 (2.9%) in those without HBV prophylaxis [17•]. The other study revealed that there were no cases of reactivation in those on HBV prophylaxis (0/5) compared to 1/7 in those without HBV prophylaxis [12].

Clinical Presentation of Those Who Developed HBVr

Table 2 presents the demographics and clinical presentation of patients who experienced HBVr. Eighteen cases of HBVr were reported, with 14 associated with ibrutinib, including two occult hepatitis B infections and 12 past HBV infections. One case was associated with zanubrutinib in HBV past infection patients, and three cases were recorded for acalabrutinib (one chronic HBV, two past HBV). Of the reported cases, 10 were observed in individuals aged over 60, compared to 7 cases in those under 60 years old. Among them, 13 were males and 4 were females. The age and sex of one patient were not reported [11]. The majority of HBVr incidents occurred within the first year after initiating BKIs. The clinical outcomes of HBVr included five cases of HBV-associated hepatitis flare, five cases of HBV-associated liver failure, six cases of asymptomatic rises in HBV DNA, and two deaths attributed to HBVr. Besides the two fatalities, HBV antiviral treatment successfully normalized liver functions and eliminated serum HBV in most cases, with only two cases experiencing suboptimal HBV control after 6 months.

Table 1 Characteristics of the observational studies of patients with past HBV infection

Author (publication time)	Definition of reactivation	No. of recruited patients	Hematologic malignancy	BTKis	Baseline HBV marker	Follow-up period (months)	No. of patients with HBV past infection (reactivation event)
No history of using rituximab or any other immunosuppressive therapies within 1 year before starting BTKIs							
Chiu et al. (2023) [19••]	AASLD 2018	82	CLL, MCL, MZL, and WM	Ibrutinib, Acalabrutinib,Zanubrutinib	HBsAg (−), HBcAb (+)	25	28(2)[a]
Hammond et al. (2018) [18]	Development of HBV DNA > 100 IU/mL on 2 consecutive measurements with or without reappearance of HBsAg in patients with evidence of past HBV infection	412	CLL	Ibrutinib	HBsAg (−), HBcAb (+), undetectable HBV DNA level	18.3	21(2)
Innocenti et al. (2022) [17•]	HBsAg seroconversion and/or an increase of serum HBV-DNA by at least one log above the lower limit of detection of the assay	108	CLL	Ibrutinib	HBsAg (−), HBcAb (+), undetectable HBV DNA level	12	35(1)
Yang et al. (2022) [16]	APASL 2016 guideline	36	CLL	Ibrutinib	HBsAg (−), HBcAb (+)	28	34(0)
Ercaliskan et al. (2019) [15]	_	27	CLL, MCL,WM	Ibrutinib	HBsAg (−), HBcAb (+), undetectable HBV DNA level	9	4(0)
Tedeschi et al. (2017) [14]	_	38	CLL	Ibrutinib	HBsAg (−), HBcAb (+), undetectable HBV DNA level	25	7(0)
Innocenti et al. (2019) [12]	AGA 2015 guideline	34	CLL	Ibrutinib	HBsAg (−), HBcAb (+), undetectable HBV DNA level	_	7(1)
Patients were on rituximab and HBV chemoprophylaxis at the time of initiating BTKIS							
Ni et al. (2022) [13]	AASLD 2018	55	R/R DLBCL	Ibrutinib, Zanubrutinib	HBsAg (−), HBcAb (+)	40	26(2[b])

CLL chronic lymphocytic leukemia, *MCL* mantle cell lymphoma, *WM* Waldenstrom macroglobulinemia, *R/R DLBCL* relapsed or refractory diffuse large B-cell lymphoma

[a]1/13 for ibrutinib and 1/14 for acalabrutinib and 0/1 for zanubrutinib

[b]1/18 for ibrutinib and 1/8 for zanubrutinib

Table 2 Characteristics of the patients who developed HBV reactivation

Author (publication time)	Age (sex)	BKIs	Timing of reactivation since initiation of BKIs (months)	Baseline hepatic marker status	HBV reactivation				HBV antiviral treatment	Clinical outcome*	Outcome of treatment
					HBsAg seroconversion	ALT/AST	Bilirubin mg/dL	Log10 HBV DNA (IU/mL)			
Lam et al. (2023) [27]	82 (F)	Ibrutinib	4	HBsAg (−), HBsAb (+), and HBcAb (+)	Yes	350/202	12	8.28	Entecavir then tenofovir	HBV-associated liver failure	Suboptimal HBV control after 6 months
Choi et al. (2023) [26]	81 (F)	Ibrutinib	12	HBsAg (−), HBsAb (+), and HBcAb (+)	Yes	170/160	NA	> 8.95	Tenofovir	HBV-associated hepatitis flare	Undetectable HBV DNA level after 6 months
de Jésus Ngoma et al. (2015) [10]	80 (M)	Ibrutinib	5	HBsAg (−), HBsAb (+), and HBcAb (+), HBV DNA level at 420 I.U/mL	Yes	103/71 (after 3 months of reactivation)	NA	7.36	Entecavir	HBV-associated hepatitis flare	Suboptimal HBV control after 6 months
Tsuruya et al. (2020) [25]	71 (M)	Ibrutinib	13	HBsAg (−), HBsAb (+), and HBcAb (+), undetectable HBV DNA level	Yes *	427/245	Normal	5.2	Entecavir then tenofovir due to lack of response	HBV-associated hepatitis flare	Undetectable HBV DNA level after 12 months
İskender et al. (2020) [24]	58 (M)	Ibrutinib	12	HBsAg (−), HBsAb (+), and HBcAb (+)	Yes	Normal	NA	8	Tenofovir	Asymptomatic rises in HBV DNA with HBsAg seroconversion	Undetectable HBV DNA level after 12 months
Adnet et al. (2021) [23]	71 (M)	Ibrutinib	16	HBsAg (−), HBsAb (+), and HBcAb (+)	Yes (it was first given false negative due to hook effect)	3086/2383	8.3	> 9	Entecavir	Death attributed to HBV reactivation	A week after starting Entecavir, hepatic encephalopathy, multiple organ failure, and death occurred

Table 2 (continued)

Author (publication time)	Age (sex)	BKIs	Timing of reactivation since initiation of BKIs (months)	Baseline hepatic marker status	HBV reactivation				HBV antiviral treatment	Clinical outcome*	Outcome of treatment
					HBsAg seroconversion	ALT/AST	Bilirubin mg/dL	Log10 HBV DNA (IU/mL)			
Malek et al. (2020) [22]	68 (M)	Ibrutinib	6	HBsAg (−), HBsAb (+), and HBcAb (+), undetectable HBV DNA	Yes	1293/872	5.3	5.82	Entecavir	HBV-associated liver failure	2 months after starting Entecavir, liver function tests normalized and HBV DNA viral load decreased
Herishanu et al. (2017) [21]	79 (M)	Ibrutinib	13.5 since initiation of Ibrutinib 1.5 M (after stopping Ibrutinib)	HBsAg (−), HBsAb (+), and HBcAb (+)		987 and 944	14.2	6.27	Tenofovir,	HBV-associated liver failure	Tenofovir gradually normalized liver functions and eliminated serum HBV DNA
Tjønnfjord et al. (2021) [20]	53 (F)	Ibrutinib	5	past infection	_	843/618	13.6	7	Tenofovir	HBV-associated liver failure	liver enzyme normalization in 3 months and HBV viral load Undetectable in 5 months
Chiu et al. (2023) [19••]	66 (M)	Acalabrutinib	21	HBsAg (−), HBsAb (+), and HBcAb (+), undetectable HBV DNA	Yes	1160/1057	10.6	8.62	Entecavir	HBV-associated liver failure	Liver enzyme normalization in 1 month and HBV viral load Undetectable in 5 months
Chiu et al. (2023) [19••]	92 (F)	Acalabrutinib	2	HBsAg (+), Anti-HBs(-)	_	135/103	0.5	7.11	Entecavir	HBV-associated hepatitis flare	Liver enzyme normalization in 2 months and HBV viral load Undetectable in 14 months
Hammond et al. (2018) [18]	57 (M)	Ibrutinib	42	HBsAg (−), and HBcAb (+), undetectable HBV DNA	No	Normal	NA	2.96	NO	Asymptomatic rises in HBV DNA without HBsAg seroconversion	

Table 2 (continued)

Author (publication time)	Age (sex)	BKIs	Timing of reactivation since initiation of BKIs (months)	Baseline hepatic marker status	HBV reactivation				HBV antiviral treatment	Clinical outcome*	Outcome of treatment
					HBsAg seroconversion	ALT/AST	Bilirubin mg/dL	Log10 HBV DNA (IU/mL)			
Hammond et al. (2018) [18]	75 (M)	Ibrutinib	22 after stopping ibrutinib	HBsAg (−), and HBcAb (+), undetectable HBV DNA	Yes	2 × normal	NA	> 8.23	Entecavir	Asymptomatic rises in HBV DNA with HBsAg seroconversion	Prompt reduction in HBV DNA
Innocenti et al. (2022) [17•]	59 (M)	Ibrutinib	3	HBsAg (−), and HBcAb (+), undetectable HBV DNA	No	Normal	NA	2.86	Entecavir	Asymptomatic rises in HBV DNA without HBsAg seroconversion	HBV-DNA became undetectable after one month of therapy
Sun (2020) et al. [11]	_	Acalabrutinib	10.3	HBsAg (−), and HBcAb (+), undetectable HBV DNA	_	_	_	8.12	Entecavir	Death attributed to HBV reactivation	The patient died of hepatic failure after 6 days
Innocenti et al. (2019) [12]	59 (M)	Ibrutinib	1.5	anti-HBs (−), and HBcAb (+), undetectable HBV DNA	No	Normal	NA	2.86	Entecavir	Asymptomatic rises in HBV DNA without HBsAg seroconversion	HBV-DNA became undetectable after five months
Ni (2022) et al. [13]	58 (M)	Ibrutinib	0.86	HBsAg (−), and HBcAb (+), detectable HBV DNA	Yes	Normal	Normal	2.27	_	Asymptomatic rises in HBV DNA with HBsAg seroconversion	_
Ni (2022) et al. [13]	49 (M)	Zanubrutinib	7.5 M after stopping zanubrutinib	HBsAg (−), and HBcAb (+), undetectable HBV DNA	-	Normal	Normal	2.62	_	Asymptomatic rises in HBV DNA	_

Death Attributed to HBV Reactivation

In their studies, Adnet et al. and Sun et al. [11, 23] documented two instances of death caused by HBVr in patients with prior HBV infection. One case was associated with using ibrutinib [23], while the other was linked to acalabrutinib [11]. Adnet et al. further reported a false-negative result for HBsAg, attributed to the hook effect, which led to a delay in providing appropriate care and hospitalizing the patient. In both instances, hepatic failure and subsequent death occurred abruptly within a week.

HBV Reactivation Following Discontinuation of BKIs

According to Herishanu et al. and Hammond et al. [18, 21], HBVr has been observed even after discontinuing ibrutinib, with reactivation occurring at 1.5 and 22 months, respectively. Another study by Ni et al. reported HBVr at 7.5 months after stopping zanubrutinib [13].

False Negativity of HBsAg Following Reactivation

False-negative HBsAg detection following reactivation was reported by Tsuruya et al. and Adnet et al. [23, 25]. In the study by Tsuruya et al. [25], false negativity of HBsAg was observed due to the presence of triple HBsAg escape mutations: Q101K, M133L, and G145A, particularly affecting the "a" determinant domain. The G145A mutation specifically reduced HBsAg production to the extent that it was undetectable using the HISCL HBsAg assay (with a detection limit of 30 mIU/mL). However, it was detectable using the LUMIPULSE HBsAg-HQ assay (Fujirebio, Tokyo, Japan) with a lower detection limit of 5 mIU/mL. In another case reported by Adnet et al. [23], falsely negative HBsAg results were initially observed due to the hook effect, which caused a falsely negative HBsAg result. This delay in accurate diagnosis led to a delay in providing appropriate care and hospitalization to the patient. Unfortunately, the patient experienced hepatic encephalopathy as well as multiple organ failure and ultimately succumbed to death attributed to HBVr, which occurred a week after starting entecavir treatment.

Discussion

To the best of our knowledge, this is the first study describing HBVr in patients receiving BTKIs. In the realm of clinical practice, there is a wide array of perspectives among physicians regarding the use of antiviral prophylaxis for patients who are receiving BTKIs. Here we are consolidating the present understanding of the risk of HBVr induced by BTKIs.

Our study highlights the following findings: (1) The rate of HBVr in patients with past HBV infection who received ibrutinib was found to be intermediate (6.6%). (2) The majority of HBVr incidents occurred within the first year after initiating BTKIs. (3) Clinical outcomes of HBVr varied, including five cases of HBV-associated hepatitis flare, five cases of HBV-associated liver failure, six cases of asymptomatic elevation in HBV DNA, and two deaths attributed to HBVr. (4) In most cases, HBV antiviral treatment successfully normalized liver functions and eliminated serum HBV, except for the two fatal cases. (5) HBV reactivation can occur even after the discontinuation of BTKIs. (6) It was also noted that the false negativity of HBsAg following reactivation could be attributed to HBsAg escape mutations or the hook effect, leading to delays in accurate diagnosis and, in some cases, resulting in death.

The occurrence of HBVr is influenced by multiple factors, including the individual's HBV serological status, level of viral replication, and the immunosuppressive potency of the drug(s) administered [2•]. For instance, patients with past HBV receiving anticancer therapies associated with an established high risk of HBVr, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy [7••].

Based on the current analysis, the rate of HBVr in patients with prior HBV infection was found to be at an intermediate level (6.6%). Universal anti-HBV prophylaxis before initiating ibrutinib may be viable; however, further data are required to substantiate this recommendation. Alternatively, a conservative approach would be to consider HBV prophylaxis in patients with a high risk of developing HBVr. It is worth noting that many case reports documenting reactivation primarily include older individuals aged 60 and males. Similarly, increased age, male sex, and extent of viral replication have been associated with HBVr during cancer chemotherapy [28].

In most cases examined in our study, the use of HBV antiviral treatment as monotherapy, specifically entecavir or tenofovir, proved successful in restoring normal liver functions and eliminating HBV from the bloodstream. However, a suboptimal control of HBV was observed even after a 6-month treatment period in the studies conducted by Lam et al. [27] and de Jésus Ngoma et al. [10]. This lack of efficacy could potentially be attributed to the presence of HBV mutations that confer resistance to the drug.

The clinical outcome of HBVr may present in a diverse spectrum of clinical manifestations, ranging from mild elevations in liver tests to severe fulminant hepatic failure, and

in some cases, even leading to death [28]. The estimated mortality rate associated with HBVr following chemotherapy is reported to range from 5 to 12% [29]. The current study reported two cases of death attributed to HBVr in patients with prior HBV infection. One case was associated with using ibrutinib, while the other was linked to acalabrutinib [11, 23]. In both instances, hepatic failure and subsequent death occurred abruptly within a week.

The occurrence of HBVr may have a delayed onset. For instance, there are reports of HBVr that occurred one year after the cessation of rituximab treatment [30]. Similarly, HBVr has been observed even after discontinuing ibrutinib, with reactivation occurring at 1.5 and 22 months, respectively [18, 21]. Another study reported HBVr at 7.5 months after stopping zanubrutinib [13]. This delayed HBVr even after cessation of immunosuppressive drugs may be related to a long period of delay for reconstitution of the recipient's immune response to HBV that may take months even after cessation of the immunosuppressive drugs [31].

Limitations

It is important to acknowledge the limitations of this study when interpreting the results. One significant limitation is the relatively small number of included studies, with some of them having small sample sizes. This can restrict the generalizability of the findings and limit the overall strength of the conclusions drawn. Therefore, further studies are necessary to gather more evidence and establish a more robust and definitive conclusion.

Future studies should prioritize investigating the risk factors or predictors associated with HBVr, the dose-dependent risk of HBVr, the potential preventive effects of high baseline anti-HBsAg levels, the additional risk associated with BTKIs in combination with anti-CD20 medications, the underlying mechanisms of increased reactivation risk, the duration of increased risk after discontinuing ibrutinib, the importance of HBV viremia without HBsAg reverse seroconversion, and the clinical significance of low-level viremia.

Conclusion

HBVr is intermediate in patients with past HBV infections who receive ibrutinib. Among the 18 cases of HBVr, most incidents occurred in males older than 60 years within the first year after initiating BTKIs, and three reported cases document the occurrence of HBVr even after the discontinuation of ibrutinib and zanubrutinib. Two cases of death in patients with past HBV infections were documented. While considering universal anti-HBV prophylaxis before initiating ibrutinib may be an option, it is essential to note that further data are required to substantiate this recommendation. Additional research is needed to provide stronger evidence regarding the potential benefits of universal anti-HBV prophylaxis in this patient population.

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Author Contribution A.Z. orchestrated the study's design and planning of this investigation. Study retrieval and screening tasks were masterfully overseen by A.Z. and validated by H.K., showcasing their meticulous approach. H.K. led data collection and analysis, with A.Z. providing cross-validation. Notably, A.A.A. played a pivotal role in collaborative data reviewing and interpretation. This synergy was further enhanced by B.O.A., S.M.H., O.Y., M.O., G.K., A.AM., and A.H., who actively contributed to data interpretation and manuscript composition. Collectively, represented by their respective abbreviations, the authors united to meticulously review and wholeheartedly endorse the final manuscript version.

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Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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- •• Of major importance

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